

Claims

1. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

(a) providing a cell having:

5 (i) a reporter gene operably linked to a DNA-binding-protein recognition site;
(ii) a first fusion gene capable of expressing a first fusion protein, said first fusion protein comprising a polypeptide fragment of Smad2 covalently bonded to a binding moiety, said binding moiety capable of specifically
10 binding to said DNA-binding-protein recognition site; and

(iii) a second fusion gene capable of expressing a second fusion protein, said second fusion protein comprising a polypeptide fragment of FAST-1 covalently bonded to a gene activating moiety;

(b) exposing said cell to said compound; and

15 (c) measuring reporter gene expression in said cell, a change in said reporter gene expression indicating said compound is capable of modulating TGF- β superfamily signalling.

2. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

20 (a) providing a cell having:

(i) a reporter gene operably linked to a DNA-binding-protein recognition site;

(ii) a first fusion gene capable of expressing a first fusion

protein, said first fusion protein comprising a polypeptide fragment of FAST-1 covalently bonded to a binding moiety, said binding moiety capable of specifically binding to said DNA-binding-protein recognition site;

(iii) a second fusion gene capable of expressing a second fusion protein, said second fusion protein comprising a polypeptide fragment of Smad2 covalently bonded to a gene activating moiety;

(b) exposing said cell to said compound; and

(c) measuring reporter gene expression in said cell, a change in said reporter gene expression indicating said compound is capable of modulating TGF- β superfamily signalling.

3. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

(a) providing a cell having:

(i) a reporter gene operably linked to a DNA-binding-protein recognition site;

(ii) a first fusion gene capable of expressing a first fusion protein, said first fusion protein comprising a polypeptide fragment of Smad3 covalently bonded to a binding moiety, said binding moiety capable of specifically binding to said DNA-binding-protein recognition site; and

(iii) a second fusion gene capable of expressing a second fusion protein, said second fusion protein comprising a polypeptide fragment of FAST-1 covalently bonded to a gene activating moiety;

(b) exposing said cell to said compound; and

(c) measuring reporter gene expression in said cell, a change in said

reporter gene expression indicating said compound is capable of modulating TGF- β superfamily signalling.

4. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

- 5 (a) providing a cell having:
- (i) a reporter gene operably linked to a DNA-binding-protein recognition site;
 - (ii) a first fusion gene capable of expressing a first fusion protein, said first fusion protein comprising a polypeptide fragment of FAST-1 covalently bonded to a binding moiety, said binding moiety capable of specifically binding to said DNA-binding-protein recognition site;
 - (iii) a second fusion gene capable of expressing a second fusion protein, said second fusion protein comprising a polypeptide fragment of Smad3 covalently bonded to a gene activating moiety;
- 15 (b) exposing said cell to said compound; and
- (c) measuring reporter gene expression in said cell, a change in said reporter gene expression indicating said compound is capable of modulating TGF- β superfamily signalling.

20 5. A cell for detecting a compound capable of modulating TGF- β superfamily signalling, said cell having:

- (a) a reporter gene operably linked to a DNA-binding-protein recognition site;
- (b) a first fusion gene capable of expressing a first fusion protein, said

first fusion protein comprising a polypeptide fragment of Smad2 covalently bonded to a binding moiety, said binding moiety capable of specifically binding to said DNA-binding-protein recognition site; and

5 (c) a second fusion gene capable of expressing a second fusion protein, said second fusion protein comprising a polypeptide fragment of FAST-1 covalently bonded to a gene activating moiety.

6. A cell for detecting a compound capable of modulating TGF- β superfamily signalling, said cell having:

10 (a) a reporter gene operably linked to a DNA-binding-protein recognition site;

(b) a first fusion gene capable of expressing a first fusion protein, said first fusion protein comprising a polypeptide fragment of FAST-1 covalently bonded to a binding moiety, said binding moiety capable of specifically binding to said DNA-binding-protein recognition site; and

15 (c) a second fusion gene capable of expressing a second fusion protein, said second fusion protein comprising a polypeptide fragment of Smad2 covalently bonded to a gene activating moiety.

7. A cell for detecting a compound capable of modulating TGF- β superfamily signalling, said cell having:

20 (a) a reporter gene operably linked to a DNA-binding-protein recognition site;

(b) a first fusion gene capable of expressing a first fusion protein, said first fusion protein comprising a polypeptide fragment of Smad3 covalently

bonded to a binding moiety, said binding moiety capable of specifically binding to said DNA-binding-protein recognition site; and

(c) a second fusion gene capable of expressing a second fusion protein, said second fusion protein comprising a polypeptide fragment of FAST-1

5 covalently bonded to a gene activating moiety.

8. A cell for detecting a compound capable of modulating TGF- β superfamily signalling, said cell having:

(a) a reporter gene operably linked to a DNA-binding-protein recognition site;

10 (b) a first fusion gene capable of expressing a first fusion protein, said first fusion protein comprising a polypeptide fragment of FAST-1 covalently bonded to a binding moiety, said binding moiety capable of specifically binding to said DNA-binding-protein recognition site; and

15 (c) a second fusion gene capable of expressing a second fusion protein, said second fusion protein comprising a polypeptide fragment of Smad3 covalently bonded to a gene activating moiety.

9. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

20 (a) providing a first polypeptide, said first polypeptide comprising a polypeptide fragment of FAST-1;

(b) providing a second polypeptide, said second polypeptide comprising a polypeptide fragment of Smad2;

(c) exposing said first polypeptide to said second polypeptide and to said

compound; and

(d) measuring the level of interaction between said first polypeptide and said second polypeptide, an alteration in said level of interaction indicating said compound is capable of modulating TGF- β superfamily signalling.

5 10. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

(a) providing a first polypeptide, said first polypeptide comprising a polypeptide fragment of Smad2;

10 (b) providing a second polypeptide, said second polypeptide comprising a polypeptide fragment of FAST-1;

(c) exposing said first polypeptide to said second polypeptide and to said compound; and

15 (d) measuring the level of interaction between said first polypeptide and said second polypeptide, an alteration in said level of interaction indicating said compound is capable of modulating TGF- β superfamily signalling.

11. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

(a) providing a first polypeptide, said first polypeptide comprising a polypeptide fragment of FAST-1;

20 (b) providing a second polypeptide, said second polypeptide comprising a polypeptide fragment of Smad3;

(c) exposing said first polypeptide to said second polypeptide and to said compound; and

(d) measuring the level of interaction between said first polypeptide and said second polypeptide, an alteration in said level of interaction indicating said compound is capable of modulating TGF- β superfamily signalling.

12. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

(a) providing a first polypeptide, said first polypeptide comprising a polypeptide fragment of Smad3;

(b) providing a second polypeptide, said second polypeptide comprising a polypeptide fragment of FAST-1;

(c) exposing said first polypeptide to said second polypeptide and to said compound; and

(d) measuring the level of interaction between said first polypeptide and said second polypeptide, an alteration in said level of interaction indicating said compound is capable of modulating TGF- β superfamily signalling.

13. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

(a) providing a reporter gene operably linked to a DNA-binding-protein recognition site;

(b) providing a first fusion protein, said first fusion protein comprising a polypeptide fragment of FAST-1 covalently bonded to a binding moiety, said binding moiety capable of specifically binding to said DNA-binding-protein recognition site;

(c) providing a second fusion protein, said second fusion protein

comprising a polypeptide fragment of Smad2 covalently bonded to a gene activating moiety;

(d) exposing said first fusion protein to said second fusion protein, to said reporter gene, and to said compound; and

5 (e) measuring the reporter gene expression, a change in said reporter gene expression indicating a compound capable of modulating TGF- β superfamily signalling.

14. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

10 (a) providing a reporter gene operably linked to a DNA-binding-protein recognition site;

(b) providing a first fusion protein, said first fusion protein comprising a polypeptide fragment of Smad2 covalently bonded to a binding moiety, said binding moiety capable of specifically binding to said DNA-binding-protein recognition site;

15 (c) providing a second fusion protein, said second fusion protein comprising a polypeptide fragment of FAST-1 covalently bonded to a gene activating moiety;

20 (d) exposing said first fusion protein to said second fusion protein, to said reporter gene, and to said compound; and

(e) measuring the reporter gene expression, a change in said reporter gene expression indicating a compound capable of modulating TGF- β superfamily signalling.

15. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

(a) providing a reporter gene operably linked to a DNA-binding-protein recognition site;

5 (b) providing a first fusion protein, said first fusion protein comprising a polypeptide fragment of FAST-1 covalently bonded to a binding moiety, said binding moiety capable of specifically binding to said DNA-binding-protein recognition site;

10 (c) providing a second fusion protein, said second fusion protein comprising a polypeptide fragment of Smad3 covalently bonded to a gene activating moiety;

(d) exposing said first fusion protein to said second fusion protein, to said reporter gene, and to said compound; and

15 (e) measuring the reporter gene expression, a change in said reporter gene expression indicating a compound capable of modulating TGF- β superfamily signalling.

16. A method for detecting a compound capable of modulating TGF- β superfamily signalling, said method comprising the steps of:

20 (a) providing a reporter gene operably linked to a DNA-binding-protein recognition site;

(b) providing a first fusion protein, said first fusion protein comprising a polypeptide fragment of Smad3 covalently bonded to a binding moiety, said binding moiety capable of specifically binding to said DNA-binding-protein recognition site;

(c) providing a second fusion protein, said second fusion protein comprising a polypeptide fragment of FAST-1 covalently bonded to a gene activating moiety;

5 (d) exposing said first fusion protein to said second fusion protein, to said reporter gene, and to said compound; and

(e) measuring the reporter gene expression, a change in said reporter gene expression indicating a compound capable of modulating TGF- β superfamily signalling.

10 17. A method for diagnosing a mammal having or likely to develop a disorder involving abnormal TGF- β superfamily signalling, said method comprising determining whether said mammal has a mutation in a gene encoding FAST-1.

15 18. A method for diagnosing a mammal having or likely to develop a disorder involving abnormal TGF- β superfamily signalling, said method comprising determining whether said mammal has an altered level of expression of FAST-1.

20 19. A substantially pure FAST-1 protein or polypeptide fragment thereof, wherein said protein or said polypeptide fragment is from a mammal, wherein said protein or polypeptide fragment is for use in modulating TGF- β superfamily signalling.

20. A substantially pure polypeptide fragment, wherein said polypeptide fragment is a polypeptide fragment of FAST-1, wherein said FAST-1

is from *Xenopus*, wherein said polypeptide fragment comprises the Smad Interaction Domain (SID), wherein said polypeptide fragment is for use in modulating TGF- β superfamily signalling.

21. A substantially pure polypeptide, wherein said polypeptide has
5 about 50% or greater amino acid sequence identity to the amino acid sequence of a substantially pure mammalian FAST-1 protein, or polypeptide fragment thereof, wherein said protein or said polypeptide fragment is for use in modulating TGF- β superfamily signalling.

22. A substantially pure polypeptide, wherein said polypeptide has
10 about 75% or greater amino acid sequence identity to the amino acid sequence of a substantially pure mammalian FAST-1 protein, or polypeptide fragment thereof, wherein said protein or said polypeptide fragment is for use in modulating TGF- β superfamily signalling.

23. A substantially pure polypeptide, wherein said polypeptide has
15 about 90% or greater amino acid sequence identity to the amino acid sequence of a substantially pure mammalian FAST-1 protein, or polypeptide fragment thereof, wherein said protein or said polypeptide fragment is for use in modulating TGF- β superfamily signalling.

24. A substantially pure nucleic acid, wherein said nucleic acid encodes
20 a mammalian FAST-1 protein, or polypeptide fragment thereof, wherein said protein or said polypeptide fragment is for use in modulating TGF- β superfamily

signalling.

25. A vector comprising a substantially pure nucleic acid, wherein said nucleic acid encodes a mammalian FAST-1 protein, or polypeptide fragment thereof, wherein said protein or said polypeptide fragment is for use in modulating TGF- β superfamily signalling, and wherein said vector is capable of directing expression of said protein or said polypeptide fragment in a cell containing said vector.

26. A vector comprising a substantially pure nucleic acid, wherein said nucleic acid encodes a FAST-1 Smad Interaction Domain (SID), wherein said SID is for use in modulating TGF- β superfamily signalling, and wherein said vector is capable of directing expression of said SID in a cell containing said vector.

27. A cell that contains a vector comprising a substantially pure nucleic acid, wherein said nucleic acid encodes a mammalian FAST-1 protein, or polypeptide fragment thereof, wherein said protein or said polypeptide fragment is for use in modulating TGF- β superfamily signalling, and wherein said vector is capable of directing expression of said protein or said polypeptide fragment.

28. A method of modulating TGF- β superfamily signalling in a cell, said method comprising providing a cell with a substantially pure FAST-1 protein, or polypeptide fragment thereof, wherein said FAST-1 protein or polypeptide fragment is provided intracellularly, and wherein said FAST-1 protein or polypeptide fragment is sufficient to modulate TGF- β superfamily signalling in a

cell.

29. A method of modulating TGF- β superfamily signalling in a cell, said method comprising introducing, into a cell, a vector comprising a substantially pure nucleic acid, wherein said nucleic acid encodes a substantially pure FAST-1 protein, or polypeptide fragment thereof, wherein said vector is
- 5 capable of directing expression of said protein or said polypeptide fragment in a cell containing said vector, and wherein expression of said FAST-1 protein or polypeptide fragment is sufficient to modulate TGF- β superfamily signalling in a cell.